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FOREWORD

Brain glycogen – vestigial no more

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Early in my career, in 1991, I was invited to a conference hosted by Leif Herz (a contributor to this issue) to present my studies on neuronal activity and astrocyte glycogen turnover. At one point I was seated near a pre-eminent scientist in the field of brain energy metabolism, and I took that opportunity to ask his thoughts about the role of glycogen in brain. His response was short and deflating: "vestigial, probably; like the appendix". As evidenced by the contributions to this Special Issue, the notion that brain glycogen is simply an evolutionary remnant, with no physiological function, has long since been put to rest. (Somewhat ironically, it turns out the appendix itself is not just "vestigial"; recent studies show that it serves as an important refuge for normal gut flora during gastrointestinal infections (Laurin et al. 2011). Nevertheless, many aspects of brain glycogen remain unresolved.

Glycogen is present in many tissue types, but it appears to have unique functional roles in brain. Liver contains the largest and most concentrated glycogen store, and this serves to maintain glucose levels in blood. Skeletal muscle contains the second most abundant store of glycogen, where it serves (at least in part) to fuel anaerobic glycolysis when muscle contractions squeeze blood from feeding arterioles and thereby limit the supply of glucose and oxygen (Greenhaff et al. 1993). Brain, however, does not serve as a glucose store for the rest of the body, nor is it is encumbered by contractions that limit blood supply. Moreover, the vast majority of brain glycogen is localized to astrocytes, rather than neurons (Cataldo and Broadwell 1986). The astrocyte glycogen undergoes continuous synthesis and degradation (Swanson et al. 1992; Watanabe and Passonneau 1973), despite the fact that this entails the additional energetic cost of one ATP for every glucose molecule that is shuttled in and out of a glycogen polymer (Obel et al. 2012). Astrocyte glycogen turnover is accelerated by neuronal activity (Cruz and Dienel 2002; Swanson 1992; Swanson et al. 1992), suppressed by anesthesia or hibernation (Swanson 1992; Watanabe and Passonneau 1973), and tightly regulated by several intersecting signaling pathways (Cambray-Deakin et al. 1988; Pellerin et al. 1997; Schorderet et al. 1984). Although these features all indicate a dynamic role for glycogen in normal brain function, it has been difficult to identify specific cellular processes that are dependent upon the astrocyte glycogen turnover.

One function of brain glycogen has been clearly demonstrated; it can be metabolized to substrates such as lactate for release from astrocytes and subsequent uptake by neurons (Brown et al. 2005; Dringen et al. 1993). This process is likely to be particularly important during severe hypoglycemia, given the unique requirement of brain for glucose as a metabolic substrate (Choi et al. 2003; Suh et al. 2007; Swanson and Choi 1993; Wender et al. 2000). However, this cannot be the whole story; severe hypoglycemia was extraordinarily rare prior to the medical use of insulin and other glucose-lowering agents, and the function of glycogen as a reserve energy supply does not account for the continuous glycogen turnover observed in normal brain. Might glycogen-derived lactate fuel neuronal function during brief, local mismatches between blood supply and energy demand in brain? Perhaps, but metabolism of lactate requires oxygen, and under any condition other than hypoglycemia in which blood delivery of glucose is insufficient to meet demand, blood delivery of oxygen will be even more limited, thus negating any advantage of lactate over blood-borne glucose as a fuel for oxidative metabolism.

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(Arterial blood normally carries around 5 mM glucose and 5 mM total oxygen, but each glucose molecule requires 6 oxygen molecules for oxidative metabolism, and each lactate requires 3 oxygen molecules for oxidative metabolism.)

More fundamentally, if brain glycogen functions to support neuronal activity, then why is glycogen stored primarily in astrocytes, rather than neurons? This question is brought into sharper focus by recent findings that small amounts of glycogen *are* present in neurons, along with all of the enzymatic activity required for regulated glycogen synthesis and degradation (Vilchez et al. 2007). Moreover, manipulations that force an increase in neuronal glycogen content lead to neuronal death, by as-yet-unresolved mechanisms (Vilchez et al. 2007). An alternatively possibility, of course, is that astrocyte glycogen might function to serve the energy needs of astrocytes themselves (as is the case in skeletal muscle). In this scenario, an advantage to the use of glycogen over glucose is that ATP can be produced much faster from glycogen. Utilization of blood glucose requires facilitated transport across cell membranes and subsequent phosphorylation at the expense of ATP, whereas glucose moieties in intracellular glycogen stores can be rapidly and directly phosphorylated using inorganic phosphate (Obel et al. 2012). The advantages of speed and local availability may facilitate astrocyte responses to the energy demands posed by the localized "bursting" nature of neuronal activity. I initially proposed this as the most likely role of astrocyte glycogen in normal brain function (Swanson 1992), but definitive support for the idea remains lacking.

More recently, there has been a growing appreciation of the how unique anatomic features of brain pose unique challenges for matching energy supply to energy demand (Dienel and Cruz 2003). One of these features is the extensive contribution of astrocyte processes to the blood–brain barrier, suggesting that most or possibly all metabolites must pass through astrocytes to gain access to neurons and other brain cell types (Abbott et al. 2006). Similarly, myelinated axons appear in both the CNS and PNS to be almost completely isolated from the extracellular space by the myelin sheath, such that the axons are dependent on metabolite delivery through the myelinating oligodendrocytes and Schwann cells (Nave 2010). A second factor is the extraordinarily reticulated nature of neuronal and glial processes, many of which are so small that they effectively exclude mitochondria. These factors raise the possibility that compartmentalization of energy metabolism within or between cell types may provide special roles for glycogen metabolism (Sickmann et al. 2005), and several of the contributions to this Special Issue address this area.

Perhaps the most exciting development in this field is the growing evidence that brain glycogen plays an essential role in learning and memory, the unique function of brain (Hertz et al. 1996; Newman et al. 2011). These reports may provide a rationale as to why glycogen metabolism in brain is so dynamically regulated, and so closely coupled to neuronal activity. It will be fascinating to see, in future studies, how glycogen metabolism in astrocytes can be biochemically linked to the neuronal processes known to subserve these unique functions of brain.

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